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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,472	03/29/2002	Eric Lam	RU-0170	3041

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,472	LAM ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Segeunce correction*.

DETAILED ACTION

Claims 1-2, 4-9 are currently at issue and are present for examination.

Applicants' amendments and arguments filed on 3-29-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the rejections under 35 U.S.C. 112, Ist paragraph and under 35 U.S.C. 102(a) and (b) in view of claim amendments.

Sequence correction by STIC

The computerized sequence information filed by the applicants has undergone a minor correction at the STIC library. A copy of the correction done is enclosed for applicant's perusal.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2, 4-9 are directed to chimeric polypeptides comprising a ß-glucuronidase reporter and repressor. Claims 1-2, 4-9 are rejected under this section of 35 USC 112 because

the claims are directed to a genus of polypeptides including modified polypeptide sequences, that have not been disclosed in the specification. No information, beyond the characterization of the function (ß-glucuronidase and its repressor, hormone binding domain) of a single species has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure and function of all the polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions and with the potentiality of generating many different antibodies. Therefore many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing that the specification clearly provides exemplary ß-glucuronidase which may be used in the chimeric protein. While this may be so, applicants have not provide the structure of wither the glucuronidase or that of the repressor domains encompassed by the claims. As discussed in the written description guidelines, the written description requirement for a claimed genus may

be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera includes species which are widely variant in structure especially the repressor domain. The genus is structurally diverse as it encompasses polypeptides with glucuronidase activity and repressor domains from a wide variety of sources. As such, the disclosure of solely functional features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus. Therefore, the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-5 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Nucleic Acids Res., Apr 15 1998, Vol. 26(8):2034-2035), Mattioni et al. (Methods in Cell Biol., Vol. 43:335-352, 1994) and Hull et al. (Methods in Mol. Biol., 1995, Vol. 49:125-141). Claims 1-2, 4-5 and 9 are specifically drawn to a fusion protein comprising a ß-glucuronidase and a hormone binding domain (HBD) linked through a predetermined protease cleavage site or sequence, wherein the ß-glucuronidase remains inactive as long as it is fused to HBD but is rendered active upon cleavage by said protease such that it is free from HBD.

Xu et al. teach in general the use of chimeric proteins comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. The reference discloses a chimeric protein comprising the green fluorescent protein (GFP) and the blue fluorescent protein (BFP) linked together through a linker comprising a spacer and a caspase cleavage sequence. The two fluorescent proteins both act as reporters and repressors of each other. The placement of the two fluorescent proteins in close

proximity reduces the fluorescence intensity compared to the intensity of the individual proteins. The cleavage by the predetermined protease such as a caspase eliminates the reduction in fluorescence. However, the reference does not teach the use of a reporter enzyme such as ß-glucuronidase and its repressor for identifying the protease of interest.

Hull et al. provide extensive information regarding the use of ß-glucuronidase as a reporter enzyme and method to use the same in reporter assays for reporting a variety of activities. From this reference it is clear to those skilled in the art that the use of ß-glucuronidase in reporter systems was well known in the art and that said enzyme was most favored for developing a reporter system.

Mattioni et al. teach regulation of protein activities by fusion to steroid binding domains. The reference teaches that an alternate method to inducible expression of a protein activity can be developed by making fusion protein, comprising the protein of interest whose activity needs to be controlled (i.e., reporter domain), and a HBD sequence linked at the N-terminal or C-terminal of the reporter protein. The reference teaches that natural ligands of the HBDs in the cell bind to the HBDs and create a stearic hindrance which renders the reporter inactive. The reference also teaches that the common HBD used is that of the example of Glucocorticoid receptor (GR), which is ubiquitously expressed in mammalian cells. The reference teaches that HSP90 binds to the GR-HBD and creates a stearic hindrance which renders any protein fused to it inactive. The reference teaches that the reporter can be activated by adding alternative ligands for the HBDs or by cleaving away the stearic hindrance which will not inactivate the reporter protein and thereby the reporter activity can be modulated. However, this reference does not

teach the use of a protease cleavage site between the HBD and reporter and the use of a protease in order to activate the reporter.

With the above references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at the instant invention. Based on the method of Xu et al. it would have been obvious to those skilled in the art to develop a fusion protein comprising a repressor domain which represses the activity of the fused polypeptide through a protease cleavage site such that upon cleavage by the protease of interest, the fused polypeptide would be rendered active and whose activity can be monitored. With such an idea in hand, it would have been obvious to those skilled in art to look for the most commonly used reporter enzyme and its repressor. Such information is provided by the combined teachings of Hull et al. which teaches the extensive use of ß-glucuronidase its use as a reporter and ways and means to monitor its activity and Mattioni et al. which provides the information regarding the use of enzyme repressors and their use in controlling enzyme activity.

With all the above teachings in hand it would have been obvious to those skilled in the art to replace the repressor and the reporter taught by Xu et al. with ß-glucuronidase and its repressor and construct a fusion protein comprising a reporter such as ß-glucuronidase and the HBD such as the GR-HBD linked through a predetermined protease cleavage site such as that of a specific caspase and use it to determine the presence of said protease. One of ordinary skill in the art would have been motivated to do so in order to develop an alternate system to that developed by Xu et al. i.e., an enzyme based fusion protein and assay as opposed to the fluorescent protein based fusion protein and assay developed by Xu et al. One of ordinary skill

in the art would have a reasonable expectation of success since all the above references teach all the important aspects of the invention.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that there is no suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the references cited. Applicants also argue that there is no expectation of success. In view of such arguments, Examiner has re-written the above rejection using the reference of Hull et al. The use of ß-glucuronidase as reporter enzyme has been documented in the art from a very long time ago. Different types of fusion proteins for detection of protease of interest has also been developed since a long time ago. All that the applicants have done is developed an alternate type of fusion protein to the one that is already well known in the art, for example the fluorescence based fusion protein of Xu et al. In the above rejection, Examiner has argued just that as the motivation which comes from the art and is not suggested by the cited references.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (Nucleic Acids Res., Apr 15 1998, Vol. 26(8):2034-2035), Mattioni et al. (Methods in Cell Biol., Vol. 43:335-352, 1994) and Hull et al. (Methods in Mol. Biol., 1995, Vol. 49:125-141) as applied to claims 1-2, 4-5, 9, and further in view of the common knowledge in the art. Claim 6-8 in this instant application are drawn to chimeric proteins for detecting the presence of predetermined protease, comprising a plurality of reporter or repressor domains or cleavage

sites, wherein the repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site.

The reference of Xu et al., Mattioni et al. and Hull et al. as it applies to chimeric proteins comprising single reporter and repressor and cleavage sites have been discussed above. Using the teachings of the above references it would have been obvious to those skilled in the art to have multiple domains such that the signal intensity obtained for the reporter domain, whether it is fluorescence as in Xu et al. reference or the activity of the reporter enzyme as in the instant case would be more intense and its detection be easier. Because of the simplicity and ease of use of the technique it would have also been obvious to one of ordinary skill in the art to use multiple protease cleavage sites and detect the presence of multiple set of proteases. One of ordinary skill in the art would have been motivated to do so in order to develop intense signal during the assay.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

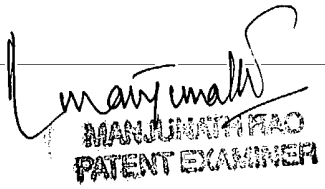
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
March 29, 2004